
Guidance for Industry

BA and BE Studies for

Orally Administered Drug

Products — General Considerations

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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**U.S. Department of Health and Human Services
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Table of Contents

I.	INTRODUCTION.....	1
II.	BACKGROUND.....	3
A.	GENERAL.....	3
B.	BIOAVAILABILITY.....	4
C.	BIOEQUIVALENCE.....	5
III.	METHODS TO DOCUMENT BA AND BE	7
A.	PHARMACOKINETIC STUDIES.....	7
B.	PHARMACODYNAMICS STUDIES	10
C.	COMPARATIVE CLINICAL STUDIES.....	10
D.	IN VITRO STUDIES	10
IV.	COMPARISON OF BA MEASURES IN BE STUDIES	11
V.	DOCUMENTATION OF BA AND BE.....	12
A.	SOLUTIONS.....	13
B.	SUSPENSIONS.....	13
C.	IMMEDIATE-RELEASE PRODUCTS: CAPSULES AND TABLETS	13
D.	MODIFIED-RELEASE PRODUCTS	14
E.	MISCELLANEOUS DOSAGE FORMS.....	18
VI.	SPECIAL TOPICS.....	18
A.	FOOD-EFFECT STUDIES	18
B.	MOIETIES TO BE MEASURED	18
C.	LONG HALF-LIFE DRUGS.....	20
D.	FIRST POINT C _{MAX}	20
E.	ORALLY ADMINISTERED DRUGS INTENDED FOR LOCAL ACTION.....	21
F.	NARROW THERAPEUTIC RANGE DRUGS	21
	APPENDIX 1: List of Guidances That Will Be Replaced.....	22
	APPENDIX 2: General Pharmacokinetic Study Design	23

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GUIDANCE FOR INDUSTRY¹

BA and BE Studies for Orally Administered Drug Products — General Considerations

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors and/or applicants planning to include bioavailability (BA) and bioequivalence (BE) information for orally administered drugs in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and their amendments and supplements submitted to the Center for Drug Evaluation and Research (CDER). This guidance addresses how to meet the BA and BE requirements set forth in 21 CFR 320 as they apply to dosage forms intended for oral administration.² The guidance should be useful for applicants planning to conduct BA and BE studies during the investigational new drug application (IND) period for an NDA, for BE studies intended for submission in an ANDA, and for BE studies conducted in the postapproval period for both ANDAs and NDAs (e.g., for certain postapproval changes).³

This guidance is one of a series of general core BA and BE guidances that are being developed that provide recommendations on how to meet provisions of 21 CFR 320 for orally administered drug products and drug products for local action. Draft guidances have been made available for public comment or are under preparation on the following topics:

- BA and BE studies for orally administered drug products (this guidance)

¹ This guidance has been prepared by the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research at the Food and Drug Administration. This guidance document represents the Agency's current thinking on methods to assess BA/BE of drug products intended for oral administration. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

² These dosage forms include solutions, suspensions, conventional, and modified (extended, delayed) release drug products.

³ Other Agency guidances are available that specifically consider specific scale-up and postapproval changes (SUPAC) for different types of drug products to help satisfy regulatory requirements in both 21 CFR part 320 and 21 CFR 314.70.

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- Average, population, and individual approaches to establishing BE⁴ (under preparation)
- Topical dermatological drug product NDAs and ANDAs — bioavailability, bioequivalence, in vitro release, and associated studies (draft published July 1998)
- Bioanalytical methods validation for human studies (draft published January 1999)
- Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on a biopharmaceutics classification system (draft published January 1999)
- Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local actions (draft published June 1999)
- Bioavailability and bioequivalence studies for oral inhalation drug products for local action: MDIs and DPIs (under preparation)

Together, the seven guidances are designed to clarify the studies needed to document product quality BA/BE for all drug products regulated by CDER in accordance with the provisions in 21 CFR 320. A further intent is to reduce regulatory burden where feasible. Although some of the guidances recommend approaches that may result in small increases in regulatory burden (e.g., a recommendation for replicate study designs in this guidance (section III.A.4)), overall the general set of approaches delineated in the general core guidances results in a substantial reduction in regulatory burden.

Once completed and finalized, these general core BA/BE guidances are designed to reduce the need for FDA drug-specific BA/BE guidances. As a result the general core BA/BE guidances may replace a number of previously issued FDA drug-specific BE guidances (see the list in Appendix 1). On rare occasions, FDA may decide to provide additional BA/BE guidance for specific drug products.

⁴ This draft guidance will update a preliminary draft guidance on the same topic published in December 1997. When finalized, this guidance will also replace an FDA guidance entitled *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design* (July 1, 1992).

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II. BACKGROUND

A. General

Studies that measure the BA and/or establish BE of a product are important elements in the support of INDs, NDAs, ANDAs, and their supplements. As part of INDs and NDAs for orally administered drug products, BA studies focus on determining the process by which a drug is released from the oral dosage form and moves to the site of action. BA data help the sponsor/applicant estimate the fraction of the drug absorbed, as well as its subsequent distribution and elimination. BA can be documented by establishing a systemic exposure profile obtained by measuring drug and/or metabolite concentration in systemic circulation over time. The systemic exposure profile determined during clinical trials in the IND period can serve as a benchmark for subsequent BE studies.

Studies to establish BE between two products are important for certain changes prior to approval in a pioneer product in NDA submissions and in the presence of certain postapproval changes in NDAs and ANDAs. In BE studies, an applicant compares the systemic exposure profile of a test drug product to that of the reference drug product. For two orally administered drug products to be bioequivalent, the active drug substance and/or active moiety in the test product should exhibit the same rate and extent of absorption as the reference drug product.

Both BA and BE studies are required by regulations, depending on the type of application being submitted. Under 21 CFR 314.94, a section on BE information is required to ensure therapeutic equivalence between pharmaceutically equivalent test and reference listed drug (reference listed drug) products. Regulatory requirements for documentation of BA and BE are provided in 21 CFR 320, which contains two subparts. Subpart A covers general provisions, while Subpart B contains 18 sections delineating the following general BA/BE requirements:

- Requirements for submission of BA and BE data (320.21)
- Criteria for waiver of an in vivo BA or BE study (320.22)
- Basis for demonstrating in vivo BA or BE (320.23)
- Types of evidence to establish BA or BE (320.24)
- Guidelines for conduct of in vivo BA studies (320.25)
- Guidelines on design of single-dose BA studies (320.26)
- Guidelines on design of multiple-dose in vivo BA studies (320.27)
- Correlations of BA with an acute pharmacological effect or clinical evidence (320.28)
- Analytical methods for an in vivo BA study (320.29)
- Inquiries regarding BA and BE requirements and review of protocols by FDA (320.30)
- Applicability of requirements regarding an IND Application (320.31)

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- Procedures for establishing and amending a BE requirement (320.32)
- Criteria and evidence to assess actual or potential BE problems (320.33)
- Requirements for batch testing and certification by FDA (320.34)
- Requirements for in vitro batch testing of each batch (320.35)
- Requirements for maintenance of records of BE testing (320.36)
- Retention of BA samples (320.38)
- Retention of BE samples (320.63)

B. Bioavailability

Bioavailability (BA) is defined in 21 CFR 320.1 as “the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.” This definition focuses on the processes by which the active ingredients and/or moieties are released from an oral dosage form and move to the site of action.

From a pharmacokinetic (PK) perspective, BA data provide an estimate of the fraction of the orally administered dose that is absorbed in systemic circulation when compared to the BA data for a solution, suspension, or intravenous dosage form (21 CFR 320.25 (d) (2) and (3)). However, BA studies can provide other useful PK information related to distribution, elimination, the effects of nutrients on absorption of the drug substance, dose proportionality, and linearity in PK of the active ingredients and/or active moieties and, where appropriate, inactive moieties.

BA data may also provide information about the properties of a drug substance prior to entry into the systemic circulation, such as permeability and the influence of presystemic metabolism and p-glycoprotein or other transporters. BA for orally administered drug products may be documented by developing a systemic exposure profile obtained by measuring the concentration of active and/or inactive moieties over time in samples collected from the systemic circulation. BA studies conducted early in the IND period provide useful information related to formulation development, the rate and extent of absorption, PK, and pharmacodynamics (PD) of the investigational drug and its metabolites (see section VI).

An explicit regulatory objective is to establish, through appropriately designed BA benchmarking studies, the performance of the formulations used in the pivotal clinical studies to demonstrate substantial evidence of safety and efficacy (320.25(d)(1)). As noted in this section, although BA studies have many PK objectives beyond formulation performance, subsequent sections of this guidance focus on BA and BE as a means to document product quality. In vivo performance, in terms of BE, may be considered one aspect of product quality that provides a link to the performance of the drug product used in pivotal clinical trials and thus to the database containing evidence of safety and

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efficacy. Systemic exposure patterns reflect both release of the drug substance from the drug product and a series of possible presystemic actions on the drug substance after its release from the drug product.

Additional comparative studies should be performed to understand the relative contribution of these two separate processes to the systemic exposure pattern. In accordance with 21 CFR 320.25(d)(2), these comparative studies may be to a solution or suspension containing the same quantity of the active drug ingredient or therapeutic moiety as the formulation proposed for marketing. Irrespective of these comparisons, noncomparative systemic exposure profiles for clinical trial materials used during the IND period can be used as a benchmark for subsequent formulation changes and may thus be useful as a reference for future BE studies. As stated at 21 CFR 320.24, a general expectation is that a formulation will be optimized for performance (BA), in the context of demonstrating safety and efficacy, during the IND period. For this reason and others, the performance of the pivotal clinical trial dosage form, as demonstrated by BA measures, may change prior to marketing the drug product.

C. Bioequivalence

Bioequivalence is defined at 21 CFR 320.1 as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." As noted in the statutory definitions, BA and BE focus on identifying the release of the drug substance from the drug product and measuring its absorption into the systemic circulation. For this reason, similar approaches to establishing BA in an NDA should generally be followed in assessing BE for an NDA or an ANDA. Establishing product quality BA is a benchmarking effort with comparisons to an oral solution, oral suspension, or an intravenous formulation. In contrast, measuring BE can be a more formal comparative test that uses specified criteria for comparisons and predetermined BE limits.

1. IND/NDAs

BE assessment may be useful during the IND/early NDA period to establish links between (1) pivotal and early clinical trial formulations; (2) formulations used in pivotal clinical trial and stability studies, if different; (3) pivotal clinical trial formulations and the to-be-marketed drug product; and (4) other comparisons, as appropriate. In each comparison, the new formulation and/or new method of manufacture is the test (T) product and the prior formulation and/or method of manufacture is the reference (R) product. The need to redocument BE during the IND period is generally left to the judgment of the sponsor, who may wish to use relevant SUPAC and dissolution guidances (see section II.C, Postapproval Changes, and III.D, In Vitro Studies) to determine when changes in components and composition and/or method of manufacture suggest a need to perform further in vitro and/or in vivo studies.

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Inequivalence in IND BE studies may arise because the test product produces higher or lower measures of rate and extent of absorption or because the performance of the test or reference is more variable. Where the test product produces levels that are substantially above (e.g., > 125 percent) those of the reference product, the regulatory concern is not therapeutic failure, but the relevance of the accumulated safety database. Where the test product produces levels that are substantially below (e.g., < 80 percent) those of the reference product, the regulatory concern becomes therapeutic efficacy. When the variability of the T rises, the regulatory concern relates to both safety and efficacy, because the T may be too variable to be useful clinically.

Proper mapping of the dose- or concentration-response curve can be useful in situations where the drug product produces levels that are either higher or lower than the reference product. In the case where levels are higher, population clinical data accumulated with higher doses may be sufficient to demonstrate that the increase in plasma levels would not be accompanied by additional risk. Similarly, population clinical data gained with lower doses may be able to demonstrate that reduced levels of the test compared to the reference product are associated with adequate efficacy. In either event, the burden is on the sponsor to demonstrate the adequacy of the clinical trials database to cover these observed deviations.

The finding of increased variability in the T product may suggest a need to reformulate, given that it suggests a drug product performing less optimally than the reference product. Frequently, nondocumentation of BE arises because of inadequate numbers of subjects in the study relative to the magnitude of intrasubject variability, and not because of either high or low relative BA of the T product. Based on these considerations, the nondocumentation of equivalence between the pivotal clinical trial formulation and the to-be-marketed formulation does not always suggest a need to reformulate and/or change the method of manufacture for the T product.

2. *ANDAs*

BE assessment is necessary in ANDA submissions to establish BE between a pharmaceutically equivalent generic drug product (T) and the corresponding reference listed drug (reference listed drug) (21 CFR 314.94(7)). Together with the determination of pharmaceutical equivalence, BE is a primary element in the determination of therapeutic equivalence.

3. *Postapproval Changes*

Information on the types of in vitro dissolution and in vivo BE studies needed for immediate release and modified release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes is provided in an FDA guidance for industry entitled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro*

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Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995); and *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (June 1997). In the presence of certain major changes in components, composition, and method of manufacture after approval, in vivo BE may need to be re-established. For approved NDAs, the drug product after the change (T) should be compared to the drug product before the change (R). For approved ANDAs, the drug product after the change (T) should be compared to the reference listed drug.

III. METHODS TO DOCUMENT BA AND BE

As noted at 21 CFR 320.24, several in vivo and in vitro methods can be used to document product quality BA and BE. In descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical, and in vitro studies. These general approaches are discussed in the following sections of this guidance. Product quality BA and BE frequently rely on pharmacokinetic measures such as AUC and Cmax that are reflective of systemic exposure.

A. Pharmacokinetic Studies

1. General Considerations

The statutory definitions of BA and BE, expressed in terms of rate and extent of absorption of the active moiety and/or ingredient to the site of action, emphasize the use of pharmacokinetic measurements in an accessible biological matrix such as blood, plasma, and/or urine to indicate the release of the drug substance from the drug product into the systemic circulation.⁵ This approach rests on an understanding that measuring the active moiety and/or ingredient at the true site of action is generally not possible and, furthermore, that some predetermined relationship between safety and efficacy has already been established relative to the concentration of active moiety and/or ingredient and/or its important metabolite or metabolites in the systemic circulation. To assess BE and product quality BA, reliance on pharmacokinetic measurements may be viewed as a bioassay that assesses release of the drug substance from the drug product into systemic circulation. A typical study is conducted as a crossover study. In this type of study, clearance, volume of distribution, and absorption, as determined by physiological variables (e.g. gastric emptying, motility, pH), are assumed to have less interoccasion variability compared to variability arising from formulation performance. Therefore, differences between the two products due to formulation factors can readily be determined.

⁵ If serial measurements of the drug or its metabolite or metabolites in plasma, serum, or blood cannot be accomplished, measurement of urinary excretion may be used to assess BE.

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2. Pilot Study

If the sponsor chooses, a pilot study in a smaller number of subjects (e.g., six) can be carried out before proceeding with a full BE study. The study can be used to validate the analytical methodology, assess variability, optimize sample collection time intervals, and provide other information. For example, for conventional immediate-release products, careful timing of initial samples may avoid a subsequent finding in a full-scale study that the first sample collection occurs after the plasma concentration peaks. For modified-release products, a pilot study can help to determine sampling times to assess lag time and dose dumping. Generally, results from a pilot study will not be useful in establishing BE.

3. Pivotal Bioequivalence Studies

General recommendations for a standard BE study based on pharmacokinetic measurements are provided in Appendix 2.

4. Replicate Study Designs

Replicate study designs (see section IV) are recommended for all BE studies using pharmacokinetic measurements, with the following exceptions: (1) BE studies of drug products containing drug substances with long half lives (e.g., > 96 hours); (2) BE studies in which a steady-state design is needed; and (3) BE studies in which excessive blood collection and/or other safety factors would arise as a result of treatment replication. For BE studies conducted during the IND period, the recommendation applies only to BE studies between the to-be-marketed dose form and pivotal clinical trial batch material. Additional justification for the use of nonreplicate study designs can be provided by sponsors and/or applicants.

5. Study Population

Unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies should be 18 years or older and capable of giving informed consent. An attempt should be made to admit as heterogeneous a study population as possible, with a reasonable balance of males and females, young and elderly, and members of differing racial groups. Restrictions on admission into the study should be based solely on safety considerations. In some instances, it may be useful to admit patients into BE studies for whom a drug product is intended. In this situation, sponsors and/or applicants should attempt to enter patients whose disease process is stable for the duration of the BE study. In accordance with 21 CFR 320.31, an IND may be required for some ANDA BE studies to help ensure patient safety.

6. Single-Dose/Multiple-Dose Studies

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Instances where multiple-dose studies may be useful are defined at 21 CFR 320.27(a)(3); however, this guidance generally recommends single-dose, pharmacokinetic BE studies for both conventional and modified-release drug products to assess BE because they are *generally* more sensitive in assessing release of the drug substance from the drug product into systemic circulation (see section V). Should a multiple-dose study design be used, appropriate dosage administration and sampling should be carried out to document attainment of steady state.

7. *Bioanalytical Methodology*

Analytical methods for BA and BE studies should be accurate, precise, specific, sensitive, and reproducible. A separate Agency guidance entitled *Bioanalytical Methods Validation for Human Studies* (published in draft for comment in January 1999) will be available, when finalized, to assist sponsors in validating bioanalytical methods.

8. *Pharmacokinetic Measures of Systemic Exposure*

Both direct (e.g., rate constant and rate profile) and indirect (e.g., C_{max}, T_{max}, mean absorption time, mean residence time, and C_{max} normalized to AUC) pharmacokinetic measurements are limited in their ability to assess rate of absorption. This guidance therefore recommends a change in focus from these direct or indirect absorption rate measurements to measurements of systemic exposure. The change in emphasis allows continued use of C_{max} and AUC as product quality BA and BE measurements, but more in terms of their capacity to assess exposure than their capacity to reflect rate and extent of absorption. Reliance on systemic exposure measurements should reflect comparable rate and extent of absorption, which in turn should achieve the underlying statutory and regulatory objective of ensuring comparable therapeutic effects. Exposure measurements are defined relative to early, peak, and total portions of the plasma, serum, and/or blood concentration-time profile, as follows.

a. Early Exposure

Early exposure in a product quality BA study can be assessed by measuring the partial area under the concentration-time profile curve with a cutoff at the peak time (T_{max}) of the drug. To establish BE, the partial area is truncated at the time of the peak of the reference formulation in each subject. A minimum of two samples should be collected before the expected peak time to allow adequate estimation of the partial area.

b. Peak Exposure

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Peak exposure should be assessed by measuring the peak drug concentration (C_{max}) obtained directly from the data without interpolation. The observed time to peak drug concentration (T_{max}) should be reported.

c. Total Exposure

For single-dose studies, the measurement of total exposure should be the:

- Area under the plasma/blood concentration-time curve from time zero to time t (AUC_{0-t}) where t is the last time point with measurable concentration
- Area under the plasma/blood concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, C_t is the last measurable drug concentration and λ_z is the terminal or elimination rate constant calculated according to an appropriate method. The terminal half-life of the drug ($t_{1/2}$) should also be reported.

For steady-state studies, the measurement of total exposure should be the area under the serum, plasma, or blood concentration-time curve from time zero to time τ over a dosing interval at steady state ($AUC_{0-\tau}$), where τ is the dosing interval.

B. Pharmacodynamics Studies

With an acceptable pharmacodynamic endpoint, suitably validated pharmacodynamic methods can be used to assess product quality BA and BE. This approach is usually not applicable to orally administered drug products where the drug is absorbed into the systemic circulation.

C. Comparative Clinical Studies

Well-controlled clinical trials in humans are useful to measure product quality BA and establish BE. The use of appropriately designed comparative clinical trials as an approach to establish BE is generally considered insensitive and should be avoided where possible (21 CFR 320.24). The comparative clinical trials approach may be called for to assess BE for orally administered drug products when measurement of the active ingredients and/or active moieties in an accessible biological fluid or pharmacodynamic approaches is infeasible.

D. In Vitro Studies

Under certain circumstances, product quality BA and BE can be documented using in vitro approaches (21 CFR 320.24). For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) may be appropriate. This approach also may be suitable in

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some circumstances in assessing BA and BE in the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved DAs and ANDAs.⁶ In addition, in vitro approaches to document BE for *nonbioproblem* drugs approved prior to 1962 remain acceptable (21 CFR 320.33).

Dissolution tests are also used to assess batch-to-batch quality, where the distribution forms the basis for a specification (test, methodology, acceptance criteria) to allow batch release. Dissolution is also used to (1) provide process control and quality assurance and (2) assess the need for further BE studies relative to minor postapproval changes, where dissolution can function as a signal of bioinequivalence. We encourage in vitro dissolution characterization for all product formulations investigated (including prototype formulations), particularly if in vivo absorption characteristics are being defined for the different product formulations. Such efforts may enable the establishment of an in vitro/in vivo correlation. When an in vitro correlation or association is available (21 CFR 320.22), the in vitro test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform in vivo. The following guidances provide recommendations on the development of dissolution test methodology, setting specifications and the regulatory applications of dissolution testing: (1) *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997); and (2) *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997).

This guidance recommends that dissolution data from three batches for both NDAs and ANDAs be used to set dissolution specifications for modified release dosage forms, including extended-release dosage forms.

IV. COMPARISON OF BA MEASURES IN BE STUDIES

An equivalence approach has been and continues to be recommended for BE comparisons. The recommended approach relies on (1) a criterion to allow the comparison, (2) a confidence interval for criterion, and (3) a BE limit for the criterion. Log-transformation of exposure measurements prior to analysis is recommended. In the past, BE studies have been performed as single-dose crossover studies in healthy volunteers. To compare measurements in these studies, data have been analyzed using an average BE criterion. More recently, new criteria to allow comparison of BE measurements have been proposed. One, termed an *individual BE criterion*, calls for study designs in which both the test and the reference drug products are administered to the same individuals on two separate occasions (replicate study design). Another, termed a *population BE criterion*, does not involve replicate study design. The recommended individual BE criterion allows assessment of both a subject-by-formulation (S*F) interaction and the within-subject variability of the test and reference products. The recommended population BE criterion allows assessment of total variability of the test and reference products but does not

⁶ A draft guidance *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System* discusses this approach (published for public comment in February 1999).

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determine the presence or absence of a S*F interaction. Both criteria allow scaling of the BE limit according to the variability of the reference product. Recommended methodologies to allow use of any of three criteria (average, population, individual BE) will be provided in an FDA draft guidance for industry on average, population, and individual approaches to establish equivalence (planned update of a preliminary draft published in December 1997).

This guidance recommends that certain in vivo BE studies conducted for (1) INDs, (2) NDAs, (3) ANDAs, and (4) amendments and supplements to NDAs and ANDAs be conducted using replicate designs (see section III.A.4). Sponsors may analyze their data using either average or population BE criteria (INDs and NDAs) or average or individual BE criteria (ANDAs and supplements to NDAs and ANDAs), provided the choice is specified in the study protocol prior to study initiation. At the sponsor's discretion, scaling may be used to judge BE when either an individual or population BE criterion is specified. Where a replicate fasting study is infeasible, sponsors are encouraged to contact appropriate review staff. In specified circumstances, replicate study designs are not needed (see III.A.4).

V. DOCUMENTATION OF BA AND BE

An in vivo study is generally recommended for all solid oral dosage forms approved after 1962 and for *bioproblem* drug products approved prior to 1962. Waiver of in vivo studies for different strengths of a drug product may be granted under 21 CFR 320.22 (d)(2) when (1) the drug product is in the same dosage form but in a different strength, and this different strength is *proportionally similar* in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an acceptable in vivo BE study; and (2) the new strengths meet an appropriate in vitro dissolution test. This guidance defines *proportionally similar* in two ways:

Definition 1: All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50 mg strength has all the inactive ingredients, exactly half that of a 100-mg strength tablet, and twice that of a 25-mg strength tablet).

Definition 2: The total weight of the tablet remains nearly the same for all strengths (within ± 5 percent of the total weight of the strength on which the biostudy was performed), the same inactive ingredients are used for all strengths, and the change in strength is obtained by altering the amount of the active ingredient and one or more of the inactive ingredients.⁷ For example, with respect to a 5-mg approved tablet, the total weight of new 1- and 2.5-mg tablets remains nearly the same, and the changes in the amount of active ingredient are offset by a change in one or more inactive ingredients. This definition is generally applicable for high-potency drug substances where the amount of active drug substance in the dosage form is relatively low (e.g., ≤ 5 mg).

⁷ The changes in the inactive ingredients should be within the limits defined by the SUPAC-IR and SUPAC-MR guidances.

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A. Solutions

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, BE can be established using nonclinical studies (21 CFR 320.22(b)(3)(i)). Solution dosage forms should not contain an inactive ingredient that may significantly affect absorption of the active drug ingredient or active moiety, either in the general population or a subpopulation (21 CFR 320.22 (b) (3) (iii)). Generally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any component that significantly affects drug absorption.

B. Suspensions

BA and BE for a suspension are generally established as for conventional release solid oral dosage forms, and both in vivo and in vitro studies are recommended.

C. Immediate-Release Products: Capsules and Tablets

1. General Recommendations

For product quality BA and BE studies, where the focus is on release of the drug substance from the drug product into the systemic circulation, a single-dose, fasting study should be performed. In vivo BE studies should be accompanied by in vitro dissolution profiles on all strengths of each product. For ANDA sponsors, the BE study should be conducted between the test product and the reference listed drug using the strength specified in *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*. For BE studies for immediate-release dosage forms where the drug product contains a narrow therapeutic range drug (see section VI.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC; (2) where an individual BE criterion is selected, reference scaling is recommended, regardless of the variability of the reference listed drug. In addition, this guidance recommends that the allowable upper limit be calculated with $\epsilon_1 = 0$ (i.e., $\theta_1 = 1.245$).

2. Exposure Measurements

For orally administered, immediate-release drug products, BE may generally be established by measurements of peak (C_{max}) and total exposure (AUC). More rapid or slower release of the active moiety and/or ingredient from a conventional/immediate release dosage form may be important clinically and, in these settings, use of an early exposure measure would be justified. At the request of a sponsor or the reviewing division, application of partial AUC as an early exposure measurement may be justified on the basis of appropriate clinical safety and/or efficacy trials and/or PK/PD studies (see section III.A.8). If the reason for an early exposure measurement can be supported, subsequent BE studies performed by either the pioneer or a generic sponsor, to include

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BE studies for postapproval change, should use the measurement for comparative analyses. If an early exposure measurement is used, statistical analysis of Cmax is not needed.

3. Biowaivers

a. INDs, NDAs, and ANDAs: Preapproval

When the drug product is the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients, using either definition of *proportionally similar* above, an in vivo BE determination of one or more lower strengths can be waived based on dissolution tests, with an in vivo study recommended only for the highest strength.⁸ Conducting an in vivo study for an ANDA on a strength that is not the highest may be appropriate for reasons of safety, subject to approval by appropriate review staff. In addition, for an NDA, biowaiver of a higher strength may be appropriate based on clinical safety and/or efficacy studies justifying the need and the dose for the higher strength. A dissolution profile should be generated for all strengths with a calculation of an f_2 criterion within a formulation. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile such that further in vivo studies are not needed. For f_2 values < 50 , further discussions with CDER review staff may help to determine whether an in vivo study is important (21 CFR 320.22 (d)(2)(ii)). In vitro dissolution profiles should also be generated for test and reference drug products at all strengths. This general approach is suitable for both NDAs and ANDAs.

b. NDAs and ANDAs: Postapproval

Information on the types of in vitro dissolution and in vivo BE studies for immediate release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes are provided in an FDA guidance for industry entitled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995). For postapproval changes, the in vitro comparison should be made between the prechange and the postchange products. In instances where dissolution profile comparisons are recommended, f_2 criteria should be used. An f_2 value of ≥ 50 suggests a sufficiently similar dissolution profile such that further in vivo studies are not needed. When in vivo BE studies are required, the comparison should be made between the prechange and postchange products for NDAs, and between postchange and the reference listed drug for ANDAs.

D. Modified-Release Products

⁸ This recommendation modifies a prior policy of allowing biowaivers for only three lower strengths on ANDAs.

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Modified-release products include delayed-release products and extended (controlled)-release products.

Delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration⁹ (i.e., these drug products exhibit a lag time in quantifiable plasma concentration). Typically, coatings (e.g., enteric coatings) are intended to delay the release of the medication until the tablet has passed through the acidic medium of the stomach. In vivo requirements for delayed-release drug products are similar to extended-release drug products. In vitro dissolution tests for these products should document that they are stable under acidic conditions and that they release the drug only in neutral medium (e.g., pH 6.8).

Extended-release drug products are dosage forms that allow a reduction in dosing frequency as compared to when the drug is presented in an immediate-release dosage form (see footnote 9). These drug products can also be developed to reduce fluctuations in plasma concentrations. Extended-release products can be developed as capsules, tablets, granules, pellets, and suspensions. If any part of a drug product includes an extended-release component, the following recommendations apply.

1. NDAs: BA and BE Studies

An NDA can be submitted for a previously unapproved new molecular entity, or for a new salt, new ester, or other noncovalent derivative of a previously approved new molecular entity, formulated as an immediate-release or extended-release drug product (Type 1 or Type 2 NDA), or as a new formulation of a previously approved NME or salt, ester, or other noncovalent derivative of a previously approved NME formulated as an immediate-release or extended-release drug product (Type 3 NDA).¹⁰ For an extended-release Type 3 NDA, if the drug product is not pharmaceutically equivalent and/or bioequivalent to a previously approved drug product (i.e., if pharmaceutically equivalent and bioequivalent), the application should be submitted as an ANDA. BA recommendations for an extended-release NDA product are considered at 21 CFR 320.25(f). The purpose for an in vivo BA study for which a controlled-release claim is made is to determine if all of the following conditions are met:

- The drug product meets the controlled release claims made for it.
- The BA profile established for the drug product rules out the occurrence of any dose dumping.

⁹ USP: *Pharmacopeial Forum*, 24 (2) 5829, 1998.

¹⁰ The types of NDAs are (1) new molecular entity (NME), (2) new ester, new salt, or other noncovalent derivative, (3) new formulation, (4) new combination, (5) new manufacturer, (6) new indication, and/or (7) drug already marketed but without an approved NDA.

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- The drug product's steady-state performance is equivalent to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

As noted at 21 CFR 320.25 (f) (2), "the reference material(s) for such a BA study shall be chosen to permit an appropriate scientific evaluation of the controlled release claims made for the drug product," such as:

- A solution or suspension of the active drug ingredient or therapeutic moiety
- A currently marketed noncontrolled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling
- A currently marketed controlled-release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling

To satisfy the CFR recommendations for BA studies for an extended-release drug product submitted as an NDA, this guidance recommends the following studies:

- A single-dose, fasting study on all strengths of tablets and highest strength of beaded capsules
- A single-dose, food-effect study on the highest strength
- A steady-state study on the highest strength

When substantial changes in the components and/or composition and method of manufacture for an extended-release drug product occur between the to-be-marketed NDA dosage form and the pivotal clinical trial material, BE studies are recommended. Generally, the type of BE studies recommended will be the same as those recommended below for an ANDA.

2. ANDAs: BE Studies

For extended-release products submitted as ANDAs, the following studies are recommended: (1) a single-dose, replicate, fasted study comparing the highest strength of the test and reference listed drug product; and (2) a food-effect, nonreplicate study comparing the highest strength of reference and test products (section VI.A). Because a single-dose study is considered more sensitive in assessing the primary question in a BE study (release of the drug substance from the drug product into the systemic circulation), a multiple-dose study is not generally recommended, even in instances where nonlinear kinetics are present. For drugs that exhibit nonlinear kinetics and/or drugs designated as

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narrow therapeutic range drugs (see section V.I.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC; (2) where an individual BE criterion is selected, reference scaling is recommended, regardless of the variability of the reference product. In addition, this guidance recommends that the allowable upper limit be calculated with $\epsilon_1 = 0$ (i.e., $\theta_1 = 1.245$). Where a replicate fasting study is infeasible, sponsors are encouraged to contact appropriate review staff.

3. *Exposure Measurements*

This guidance recommends that early and total exposure measurements be analyzed in single-dose studies for modified-release drug products.

4. *Biowaivers: NDAs and ANDAs*

When the extended-release drug product is the same dosage form and employs, for lower strengths, the same drug release mechanism, and where the lower strengths are proportionally similar in active and inactive ingredients, using either definition of *proportionally similar* above, an in vivo BE determination of one or more lower strengths can be waived based on dissolution tests.

a. *Beaded Capsules - Lower Strength*

For extended-release beaded capsules where the strength differs only in the number of beads containing the active moiety, the single-dose, fasted, in vivo BE study needs to be carried out only at the highest strength, with waiver of in vivo, single-dose, fasted studies for lower strengths based on dissolution profiles. A dissolution profile should be generated for all strengths with the calculation of an f_2 criterion within a manufacturer. An f_2 value ≥ 50 can be used to confirm that further in vivo studies are not needed.

b. *Tablets - Lower Strength*

For extended-release tablets when the drug product is the same dosage form but in a different strength, is proportionally similar in its active and inactive ingredients, and has the same drug release mechanism, an in vivo BE determination of one or more lower strengths can be waived based on dissolution profile comparisons, with an in vivo study only on the highest strength. The drug products should exhibit similar dissolution profiles between the highest strength and the lower strengths based on f_2 metric in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8). The dissolution profile should be generated on the test and reference drug products at all strengths.

5. *Postapproval Changes*

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Information on the types of in vitro dissolution and in vivo BE studies for extended-release drug products approved as either NDAs or ANDAs in the presence of specified postapproval changes are provided in an FDA guidance for industry entitled *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (SUPAC-MR)* (October 1997). For the postapproval changes, the comparison should be made between the prechange and the postchange products. In instances where dissolution profile comparisons are recommended, the f_2 criterion should be used. An f_2 value of ≥ 50 suggests a similar dissolution profile. When in vivo BE studies are conducted, the comparison should be made between the prechange and postchange products for NDAs, and between postchange and Reference listed drug for ANDAs.

E. Miscellaneous Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for in vitro dissolution and in vivo BE. Chewable tablets should also be evaluated for in vivo BE. Chewable tablets should be studied for in vitro dissolution tests under the same conditions as nonchewable tablets of the same active moiety, because they might be swallowed by a patient without proper chewing.

VI. SPECIAL TOPICS

A. Food-Effect Studies

Coadministration of food with oral drug products may influence drug BA and/or BE. Food-effect BA studies focus on the effects of food on the absorption of the drug substance as well as the release of the drug substance from the drug product. BE studies with food focus on demonstrating comparable BA between test and reference products when coadministered with meals. Usually, a single-dose, two-period, two-treatment, two-sequence crossover study is recommended for both food-effect BA and BE studies.¹¹

B. Moieties to Be Measured

1. Parent Drug Versus Metabolites

The moieties to be measured in BA and BE studies are the active drug ingredient or active moiety in the administered dosage form and, when appropriate, its active metabolites (21 CFR 320.24(b)(1)(i)). This guidance recommends the following approaches for BA and BE studies.

¹¹ A draft guidance for industry, *Food Effects Bioavailability and Bioequivalence Studies*, which was issued in October 1997 and currently is being finalized, addresses studies to be carried out when a product is labeled to allow mixing with food prior to administration.

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For BA studies (see section II.B), determination of moieties to be measured in the administered dosage form should take into account both concentration and activity. *Concentration* refers to the quantity of the active ingredient and/or active moiety and one or more metabolites per milliliter in an accessible biological fluid such as blood or plasma. *Activity* refers to the in vivo contribution of the active ingredient and/or active moiety in the administered dosage form and/or metabolite to the safety and/or efficacy of the drug. In this approach, both the active ingredient and/or active moiety and active metabolites should be measured, if analytically feasible.

For BE studies, determination of only the active moiety and/or active ingredient in the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration-time profile of the active moiety in the dosage form is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. The following are exceptions to this general approach.

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable measurement in blood, plasma, or serum.
- In certain circumstances, a degradant may be formed in the lumen of the gastrointestinal tract and/or a metabolite may be formed after absorption as a result of gut wall or other prehepatic metabolism. If the fraction of degradant and/or metabolite is low, small differences in the release of an active moiety and/or active ingredient from a dosage form may become important because of differentials in levels of degrading and/or metabolizing systems throughout the gastrointestinal tract. When the degradant and/or metabolite does not contribute meaningfully to safety and/or efficacy, neither needs to be measured. If the degradant and/or metabolite contributes meaningfully to safety and/or efficacy, the degradant and/or metabolite should be measured to ensure bioequivalence. Based on these considerations, a degradant formed in the lumen of the gastrointestinal tract or a metabolite formed as a result of gut wall or other prehepatic metabolism should be measured, in addition to measurement of the active moiety and/or active ingredient, when (1) the fraction of the active moiety and/or active ingredient transformed to the degradant and/or metabolite is low (< 20 percent); and (2) the absorbed degradant and/or metabolite contributes meaningfully (e.g., > 20 percent of total activity) to the safety and/or efficacy of the administered drug product. Determination of a meaningful contribution of a degradant and/or metabolite to safety and/or efficacy can be based on literature data and/or approved product labeling statements indicating important activity.

2. Enantiomers Versus Racemates

For BA studies, measurement of both enantiomers may be important. For BE studies, this guidance recommends measurement of the racemate using an achiral assay, without measurement of individual enantiomers. However, measurement of individual

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enantiomers in BE studies is recommended when all of the following conditions are met: (1) the enantiomers exhibit different pharmacodynamic characteristics; (2) the enantiomers exhibit different pharmacokinetics; (3) the primary activity resides with the minor enantiomer, defined as having < 20 percent of the total of all the enantiomer AUC; and (4) nonlinear absorption is present (as expressed by a change in the enantiomer's concentration ratio with change in the input rate of the drug) for at least one of the enantiomers. In such a case, BE criteria should be applied to both enantiomers.

3. Drug Products With Complex Mixtures as the Active Ingredient

Certain drug products may contain complex drug substances (i.e., active moieties and/or active ingredients that are mixtures of multiple synthetic and/or natural source components). Some or all of the components of these complex drug substances may not be characterized with regard to chemical structure and/or biological activity. Quantification of all active or potentially active components in pharmacokinetic studies to document BA/BE is neither necessary nor desirable. Rather, BA and BE pharmacokinetic studies should be based on a small number of markers of rate and extent of absorption. Although necessarily a case-by-case determination, criteria for marker selection include amount of the moiety in the tablet, plasma, or blood levels of the moiety, relative to other moieties in the complex mixture, and biological activity. Where pharmacokinetic approaches are not feasible to assess rate and extent of absorption of a complex drug substance from a drug product, in vitro approaches may be preferred. Rarely, pharmacodynamic or clinical approaches may be called for if no quantifiable moieties are available for in vivo pharmacokinetic or in vitro studies.

C. Long Half-Life Drugs

In a BA/PK study involving a long half-life drug product, adequate characterization of the half-life calls for blood sampling over a long period of time. For BE determination of long half-life drug products, a nonreplicate, single-dose, crossover study can be conducted, provided an adequate washout period is used. If the nonreplicate, crossover study is problematic, a parallel BE study design can be used. For a crossover or parallel study design, sample collection time should be adequate to ensure completion of the drug product's gastrointestinal transit (approximately 2 to 3 days) and drug absorption. In addition, if the drug distribution and elimination are similar for the two products (i.e., intra/intersubject variation is low), C_{max} and a suitably truncated AUC should be used to adequately characterize the rate and extent of absorption. Alternatively, whenever intra/intersubject variations in distribution and elimination are high, truncated AUCs should result from a similar amount of truncation for each subject's plasma concentration-time curve.

D. First Point C_{max}

The first point in a concentration-time curve in a BE study based on blood and/or plasma measurements is sometimes the highest point, raising a concern that the peak

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concentration has been missed because of insufficient early sampling. A carefully conducted pilot study may help avoid this problem. Collection of an early time point between 5 and 15 minutes after dosing, followed by at least an additional two sample collections in the first hour after dosing may be sufficient to assess early peak concentrations. When this sampling approach is followed, data sets should be considered adequate, even when the first time point is the highest observed concentration.

E. Orally Administered Drugs Intended for Local Action

Documentation of product quality BA for NDAs where the drug substance produces its effects by local action in the gastrointestinal tract can be achieved using clinical safety and efficacy studies and suitably designed and validated in vitro studies. Similarly, documentation of BE for ANDAs, and both NDAs and ANDAs for certain postapproval changes, can be achieved using clinical efficacy and safety studies and/or suitably designed and validated in vitro studies where the latter are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study. To ensure comparable safety, additional studies with and without food may help to understand the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.

F. Narrow Therapeutic Range Drugs

This guidance, as do some other FDA and USP documents, recommends additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range¹² drugs (see sections V.C and D). The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs. It is not designed to influence the practice of medicine or pharmacy. Where specified in this and other Agency BA/BE guidances, this guidance defines narrow therapeutic range drug products as those containing drug substances that are subject to therapeutic drug monitoring and/or where product labeling specifies that the drug is an narrow therapeutic range drug. Examples include: digoxin, fentanyl (transdermal), lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug monitoring are narrow therapeutic range drugs, sponsors/applicants should contact the appropriate review division at CDER to determine whether a drug should or should not be considered narrow therapeutic range.

¹² This guidance uses the term narrow therapeutic range instead of narrow therapeutic index drug, although the latter is more commonly used.

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APPENDIX 1: List of Guidances That Will Be Replaced

1. Division of Biopharmaceutics *Guidelines for the Evaluation of Controlled Release Drug Products* (April 1984).
2. *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design* (July 1992).
3. *Oral Extended (Controlled) Release Dosage Form: In Vivo Bioequivalence and In Vitro Dissolution Testing* (September 1993).
4. Preliminary draft guidance for industry, *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (December 1997).
5. Drug specific bioequivalence guidances from the Division of Bioequivalence, Office of Generic Drugs, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, FDA.

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APPENDIX 2: General Pharmacokinetic Study Design

For both replicate and nonreplicate, in vivo, pharmacokinetic BE studies, the following general approaches are recommended, recognizing that the elements may be adjusted for certain drug substances and drug products.

Study conduct:

- The test or reference products should be administered with 240 ml of water to an appropriate number of subjects.
- Generally, the highest marketed strength should be administered as a single unit. If necessary for analytical reasons, multiple units of this highest strength can be administered, providing the total single-dose remains within the labeled dose range.
- An adequate washout period should separate each treatment.
- The lot numbers of both test and reference listed products and the expiration date for the reference product should be stated. The drug content of the reference listed product should not differ from that of the test product by more than 5 percent. The sponsor should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of test and reference listed products. In accordance with 21 CFR 320.38, samples of the test and reference listed product must be retained for 5 years.
- Prior to and during each study phase, subjects should (1) be allowed water as desired except for one hour before and after drug administration; (2) be provided standard meals no less than 4 hours after drug administration; (3) abstain from alcohol for 48 hours prior to each study period and until after the last sample from each period is collected.

Sample collection and sampling times:

- Under normal circumstances, blood, rather than urine or tissue, should be used. In most cases, drug, or metabolites are measured in serum or plasma. However, in certain cases whole blood may be more appropriate for analysis. Blood samples should be drawn at times that can be used to describe the absorption, distribution, and elimination phases of the drug. For most drugs, 12 to 18 samples, including a predose sample, should be collected per subject per dose. This sampling should continue for at least three or more terminal half-lives of the drug. The exact times for sample collection depend on the nature of the drug and the input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration of the drug in the blood (C_{max}), terminal

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elimination rate constant (K_{el}), and at least 80 percent of the known area under the curve to infinity ($AUC_{0-\infty}$) can be estimated accurately. At least three to four samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of the terminal elimination rate constant from linear regression. The actual clock times when samples are drawn as well as the elapsed time related to drug administration should be recorded.

Subjects with predose plasma concentrations:

- If the predose concentration is less than or equal to 5 percent of C_{max} value in that subject, the subject's data can be included in all pharmacokinetic measurements and calculations. If the predose value is greater than 5 percent of C_{max} , the subject should be dropped from all BE study evaluations.

Pharmacokinetic information recommended for submission:

- Pharmacokinetic parameter or the metric being calculated
- Plasma concentrations and time points
- Subject, period, sequence, treatment, AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} , and half-life,
- Systemic exposure measurements: Early (Partial AUC), Peak (C_{max}), and Total ($AUC_{0-\infty}$)
- Statistical Information on AUC_{0-t} , $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, C_{max} , T_{max} , K_{el} , half-life, $\ln AUC_{0-t}$, $\ln AUC_{0-\infty}$, and $\ln C_{max}$: geometric mean, arithmetic mean, ratio of means, and confidence intervals
- Intersubject, intrasubject, and/or total variability, if available
- Subject-by-formulation interaction variance component (σ_D^2), if individual BE criterion is used
- C_{min} , C_{av} , and degree of fluctuation, if steady-state studies are employed. Evidence of attainment of steady state should be provided.

Rounding off of confidence interval values:

- Confidence interval (CI) values should not be rounded off; therefore, to pass a CI limit of 80-125, the value should be at least 80.00 and not more than 125.00.